

BE
Please add new claims 24-33 as follows:

24. The method of Claim 1, wherein said administering is local, systemic, topical, subcutaneous, intradermal, or transdermal.
25. The method of Claim 1, wherein said cutaneous lymphocyte-associated antigen memory T-cell moves into the dermis or epidermis of said skin.
26. The method of Claim 22, wherein said skin disorder is inflammation.
27. The method of Claim 22, wherein said skin disorder is allergic-contact dermatitis.
28. The method of Claim 22, wherein said skin disorder is psoriasis.
29. The method of Claim 22, wherein said skin disorder is wound healing.
30. The method of Claim 22, wherein said skin disorder is cancer.
31. The method of Claim 22, wherein said skin disorder is carcinoma.
32. The method of Claim 22, wherein said skin disorder is infection.
33. The method of Claim 32, wherein said infection is microbial, viral, or parasitic.

REMARKS

SPECIFICATION

The specification has been amended to update the status of the parent nonprovisional application. The specification has also been amended to update the status of the patent applications referenced throughout the disclosure. In addition, an embedded hyperlink within the specification has been deleted.

TITLE

As suggested by the Examiner, the title has been revised to more clearly reflect the subject-matter of the presently claimed invention.

STATUS OF CLAIMS

Claims 2 and 23 have been cancelled.

Applicants have amended claims 1, 3, 4 and 22 for greater clarity. In addition, new claims 24-25 (corresponding to claims 3(b), 3(e), respectively) and 26-33 have been added. Support for these claim amendments and new claims can be found in the specification and the originally filed claims. For example, support for claims 24-25 can be found in originally filed claim 3; and support for claims 26-33 can be found on page 10, lines 4-9. No new matter has been added.

Applicants attach Appendix A with the newly revised claims, primarily for the Examiner's convenience.

In addition, Applicants attach Appendix B which is a marked-up version of the changes made to the claims by the current amendments.

REJECTIONS UNDER 35 U.S.C. § 112, first paragraph

Claims 1-4 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement. As noted above, claim 2 has been cancelled. The rejection of claims 1, 3 and 4 is addressed below.

The Examiner notes that the specification is "enabling for a method of impairing movement of a CLA+ memory T cell within or to the skin of a mammal, said method comprising locally, topically, intradermally, or transdermally administering to said mammal an effective amount of an antibody against CTACK, wherein said antibody impairs movement of a cutaneous lymphocyte-associated antigen (CLA)+ memory T cell within or to the skin of a mammal."

Amended claim 1 (from which claims 3 and 4 depend) reads as follows:

A method for impairing movement of a cutaneous lymphocyte-associated antigen⁺ (CLA⁺) memory T-cell within or to the skin of a mammal, said method comprising administering to said mammal an effective amount of an antibody against cutaneous-T-cell-attracting chemokine (CTACK), whereby administration of said antibody impairs movement of said cutaneous lymphocyte-associated antigen⁺ memory T-cell within or to the skin of said mammal.

Amended claim 3 (corresponding to the subject-matter of claim 3(a)) reads as follows:

The method of Claim 1, wherein said movement is within said skin.

Amended claim 4 (corresponding to the subject-matter of claim 4(a)) reads as follows:

The method of Claim 1, wherein said antibody neutralizes cutaneous-T-cell-attracting chemokine.

New claim 24 (corresponding to the subject-matter of claim 3(b)) reads as follows:
The method of Claim 1, wherein said administering is local, systemic, topical, subcutaneous, intradermal, or transdermal.

New claim 25 (corresponding to the subject-matter of claim 3(e)) reads as follows:
The method of Claim 1, wherein said cutaneous lymphocyte-associated antigen⁺ memory T-cell moves into the dermis or epidermis of said skin.

Claim 1 (from which claims 3, 4, 24 and 25 depend) has been amended by replacing the term “modulating” with the term “impairing.” In addition, claim 1 has been amended by specifying that the cell is a cutaneous lymphocyte-associated antigen (CLA)+ memory T cell, and that the antagonist of cutaneous-T-cell-attracting chemokine (CTACK) is an antibody against CTACK. Lastly, claim 1 has been amended by including a step that clearly relates back to the preamble (*i.e.*, that administration of the antibody against CTACK impairs movement of the cutaneous lymphocyte-associated antigen memory T-cell within or to the skin of the mammal).

Claim 3 has been amended such that it is directed solely to the subject-matter of claim 3(a). New claims 24 and 25 correspond to the subject-matter of claim 3(b) and 3(e), respectively. The subject-matter of claims 3(c) and 3(d) has been incorporated into amended claim 1.

Claim 4 has been amended such that it is directed solely to the subject-matter of claim 4(a). The subject-matter of claim 4(b) and 4(c) has been cancelled.

Applicants note that contrary to the Examiner’s allegation, the specification discloses that a CTACK antagonist is administered systemically to a mammal. See, for example, page 3, lines 7-13. Applicants also note that Petitt *et al.*, *Trends Biotechnol.*, **16**:343-349 (1998), (page 343, columns 1-2; and page 345, column 2) has been misinterpreted. It is true that proteins have a variety of properties that do not allow them to be delivered non-invasively. By non-invasively however, the authors refer to application of proteins to the skin or the taking of proteins orally. In contrast, it is a clinically accepted method to inject the patient (*i.e.*, an invasive procedure) and deliver a solution of proteins either into the vein (*i.v.*) or into the subcutaneous compartment (*s.c.*). Delivery by the *i.v.* route or *s.c.* route will result in systemic delivery to all tissues because the *s.c.* fluid drains into the blood system via the lymphatic system. The following articles, copies of which are enclosed herein, demonstrate the administration of a protein antagonist (*e.g.*, an antibody) by these two routes.

- Elliott *et al.*, *Arthritis and Rheumatism*, **36**(12):1681-1690 (1993)
Clinical trial to test the safety and efficacy of treating rheumatoid arthritis patients with an antibody antagonist to the cytokine TNF.
p1683/column 2: The treatment protocol states that the antagonistic antibody is delivered intravenously (*i.e.*, systemically) and was efficacious at a distal site (*i.e.*, the inflamed joint).
- Moreland *et al.*, *New England J. of Medicine*, **337**(3):141-147 (1997)
Clinical trial to test the safety and efficacy of treating rheumatoid arthritis patients with a protein antagonist of the cytokine TNF.
p141/column 2: The treatment protocol states that the antagonistic protein is delivered subcutaneously (*i.e.*, systemically) and was efficacious at a distal site (*i.e.*, the inflamed joint).

- Pugsley, *Current Opinions in Investigational Drugs*, **2(12)**:1725-1731 (2001)
Review of Etanercept (protein antagonist of TNF).
p1727/column 1: Phase 1 arthritis clinical trial protocol states that the antagonistic protein is delivered intravenously (*i.e.*, systemically).
- Keating *et al.*, *Biodrugs*, **16(2)**:111-148 (2002)
Review of infliximab (antagonistic antibody to TNF) to treat arthritis and Crohn's disease.
p121/column 2: A single intravenous infusion was effective at inducing a response in active refractory Crohn's patients.

Based on the state of the art evidenced in the articles cited above, the administration of antibodies systemically (*e.g.*, by subcutaneous injection) is a routinely used for the administration of protein antagonists and would not require undue experimentation by one of skill in the art.

In light of the above arguments and amendments, claims 1, 3, 4, 24 and 25 are believed to be enabled by the specification. As such, Applicants respectfully request withdrawal of this rejection under 35 U.S.C. § 112, first paragraph.

Claims 22-23 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement. Claim 23 has been cancelled. The rejection of claim 22 is addressed below.

Amended claim 22 reads as follows:

A method for treating a patient suffering from a skin disorder comprising administering an effective amount of an antibody against cutaneous-T-cell-attracting chemokine.

Claim 22 has been amended by replacing the term “antagonist” with the term “antibody,” and by replacing the abbreviation “CTACK” with the phrase “cutaneous-T-cell-attracting chemokine.”

Applicants note that contrary to the Examiner's allegation, the specification discloses treating a patient suffering from a skin disorder by administering an antagonist against CTACK. See, for example, page 5, lines 8-11 and page 10, lines 5-9.

Likewise, contrary to the Examiner's allegation, the specification also provides guidance as to what skin disorders should be treated by CTACK. The specification discloses that CTACK production is up-regulated by the pro-inflammatory cytokines TNF- α /IL-1 β *in vitro* and down-regulated by (anti-inflammatory) glucocorticosteroids *in vivo* (apparently via NF κ B and I κ B). Notably, the pro-inflammatory cytokine, TNF- α plays a dominant role in the pathogenesis of inflammatory and autoimmune diseases, including rheumatoid arthritis, Crohn's diseases and

psoriasis (see, e.g., Bondeson and Maini, *Int J Clin Prac*, 55:211-216; and Kirby *et al.*, *Clin Exp Dermatol*, 26:27-29 (2001); copies of which are enclosed herein). Furthermore, the specification discloses that *in vivo* neutralization of CTACK/CCR10 interactions impair lymphocyte recruitment to the skin such that allergen-induced skin inflammation is suppressed. Moreover, neutralization of CTACK was shown to be superior to the topical immunosuppressant FK506/tacrolimus in inhibiting antigen-specific skin inflammation. See, for example, on page 12, lines 12-29.

The specification discloses that CTACK appears to be a homeostatic chemokine whose expression is regulated by the differentiation stage of its cell of origin and by inflammatory processes. CTACK/CCR10 interactions appear to play an important role in skin homeostasis and the initiation of skin inflammation. See, for example, page 12, line 30 to page 13, line 15. The specification further discloses that CTACK will find use in affecting medical abnormalities of the skin. In particular, the following skin disorders involved in the immune system are listed: psoriasis, skin cancers, carcinomas, inflammation, allergies, contact and allergic dermatitis, wound healing, infections (including microbial, viral, and parasitic). See, for example, page 10, lines 3-9.

In addition, Homey *et al.*, *Nature Medicine*, 8:157-165 (2002) (cited by the Examiner as being pertinent to Applicant's disclosure) demonstrate that patients suffering from psoriasis, atopic or allergic-contact dermatitis express CCR10 (the receptor for CTACK), and that neutralization of CCL27/CCR10 interaction impaired lymphocyte recruitment to the skin. Thereby, leading to the suppression of allergen-induced skin inflammation.

In light of the above amendment, Applicants respectfully request withdrawal of this rejection under 35 U.S.C. § 112, first paragraph.

REJECTIONS UNDER 35 U.S.C. § 112, second paragraph

Claims 1-4 and 22-23 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject-matter which Applicants regard as the invention.

Claims 1, 4 and 22 have been amended by replacing the term "CTACK" with the term "cutaneous-T-cell-attracting chemokine." Likewise, claim 1 has been amended by replacing the term "CLA+" with the term "cutaneous lymphocyte-associated antigen".

The subject-matter of claim 3(e) (corresponding to new claim 25) has been amended by replacing the term "and/or" with the term "or."

As noted above, claim 1 (from which claims 3, 4, 24 and 25 depend) has been amended by including a step that clearly relates back to the preamble (*i.e.*, that administration of the antibody against CTACK impairs movement of the cutaneous lymphocyte-associated antigen memory T-cell within or to the skin of the mammal).

As such, Applicants respectfully request withdrawal of this rejection under 35 U.S.C. § 112, second paragraph.

CONCLUSION

Applicants reserve the right to file subsequent applications claiming the non-elected subject-matter and do not waive any of their rights or abandon any non-elected subject-matter. It is believed that the foregoing amendment places this application now in condition for early action. Therefore, early and favorable action allowing pending claims 1, 3, 4, 22, and 24-33 is respectfully solicited.

Respectfully submitted,



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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION

Prior to the first sentence of the specification, please include the following:

This is a continuation-in-part of U.S. Application No. 09/471,549, filed December 23, 1999, now abandoned.

At the top of pages 1 and 102, please replace the present title with the following:

METHOD OF IMPAIRING MOVEMENT OF A CLA⁺ MEMORY T-CELL WITHIN OR TO THE SKIN OF A MAMMAL BY ADMINISTERING A CTACK ANTAGONIST.

On page 9, lines 3-20, please replace the present pending text with the following:

The described chemokines or receptors should be important for mediating various aspects of cellular, organ, tissue, or organismal physiology or development. In particular, the Vic chemokine is a classic pro-inflammatory chemokine, which mediates inflammatory processes. The CTACK is a cutaneously expressed chemokine. See, e.g., USSN 08/978,964 (now abandoned) and related cases.

In contrast to naive lymphocytes, memory/effector lymphocytes can access non-lymphoid effector sites and display restricted, often tissue-selective, migration behavior. The cutaneous lymphocyte-associated antigen (CLA) defines a well described subset of circulating memory T cells that selectively localize in cutaneous sites mediated in part by the interaction of CLA with its vascular ligand E-selectin. Picker, et al. (1991) Nature 349:796-799; and Rossiter, et al. (1994) Eur. J. Immunol. 24:205-210. E-selectin is broadly expressed in inflamed endothelium; thus, specific infiltration of skin by CLA⁺ cells must require additional cues. Herein is description of particular C-C chemokines, one originally designated GWCC but herein referred to as CTACK, and the other Vic. See USSN 08/978,964 (now abandoned) or WO 98/23750, which are incorporated herein by reference for all purposes.

On page 20, line 31 to page 21, line 5, please replace the present pending text with the following:

Mammalian CTACK chemokines were described previously in USSN 08/978,964 (now abandoned), which describes various migratory assays. Various agonists and antagonists of the natural ligands can be produced. The migration assays may take advantage of the movement of cells through pores in membranes. Chemotaxis may be measured thereby. Alternatively, chemokinetic assays may be developed, which measure the induction of kinetic movement, not necessarily relative to a gradient, *per se*.

On page 62, lines 19-31, please replace the present pending text with the following:

The human or mouse CTACK sequence is readily available. See SEQ ID NO: 11 or 13, respectively. Appropriate PCR primers or hybridization probes can be selected. Likewise for GPR2 and Vic (SEQ ID NO: 1,3, 5, 7, and 9) sequence analysis. TBLASTN searches of a proprietary and Genbank dbEST databases, with the sequences of known CC chemokines, identified the ESTs for human and murine CTACK, respectively. Murine CTACK cDNA, IMAGE consortium clone #316475, was obtained from Genome Systems as an EcoRI-NotI insert in the pT7T3-PacD vector. Human CTACK was obtained as a Sall-NotI insert in the pSPORT 3.0 vector. The nucleotide sequence of both clones was confirmed by automated sequencing. The signal peptide cleavage sites were predicted using the SignalP server (<http://www.cbs.dtu.dk/services/SignalP/>). Sequences were aligned using CLUSTAL W.

IN THE CLAIMS

1. A method of modulating impairing movement of a cutaneous lymphocyte-associated antigen (CLA⁺) memory T-cell within or to the skin of a mammal, said method comprising administering to said mammal an effective amount of an antagonist antibody of against CTACK cutaneous-T-cell-attracting chemokine (CTACK), whereby administration of said antibody impairs movement of said cutaneous lymphocyte-associated antigen⁺ memory T-cell within or to the skin of said mammal.
2. The method of Claim 1, wherein modulating is blocking and administering is an antagonist of CTACK.
3. The method of Claim 2 1, wherein:
 - a) said movement is within said skin;
 - b) said administering is local, systemic, topical, subcutaneous, intradermal, or transdermal;
 - c) said administering is an antagonist of CTACK;
 - d) said cell is a CLA⁺ cell; or
 - e) said cell moves into the dermis and/or epidermis layers of said skin.
4. The method of Claim 2 1, wherein:
 - a) said antagonist is an antibody which neutralizes CTACK cutaneous-T-cell-attracting chemokine;
 - b) said mammal is subject to a transplant or skin graft;
 - c) said antagonist is administered in combination with an antibiotic.

22. A method of for treating a patient suffering from a skin disorder comprising administering an effective amount of an antagonist antibody against CTACK cutaneous-T-cell-attracting chemokine.
23. The method of Claim 22, wherein the antagonist is an antibody.
24. The method of Claim 1, wherein said administering is local, systemic, topical, subcutaneous, intradermal, or transdermal.
25. The method of Claim 1, wherein said cutaneous lymphocyte-associated antigen memory T-cell moves into the dermis or epidermis of said skin.
26. The method of Claim 22, wherein said skin disorder is inflammation.
27. The method of Claim 22, wherein said skin disorder is allergic-contact dermatitis.
28. The method of Claim 22, wherein said skin disorder is psoriasis.
29. The method of Claim 22, wherein said skin disorder is wound healing.
30. The method of Claim 22, wherein said skin disorder is cancer.
31. The method of Claim 22, wherein said skin disorder is carcinoma.
32. The method of Claim 22, wherein said skin disorder is infection.
33. The method of Claim 32, wherein said infection is microbial, viral, or parasitic.